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Case Report

Nintedanib-Induced Delayed Mucosal Healing after Adjuvant Radiation in a Case of Oropharyngeal Carcinoma

Satoru Takahashi[a] Masashi Endo[a] Yukiko Fukuda[a] Kazunari Ogawa[a] Michiko Nakamura[a] Kohei Okada[a] Masahiro Kawahara[b] Keiko Akahane[b] Takafumi Nagatomo[c] Ryutaro Onaga[c] Hiroshi Nishino[c] Harushi Mori[a] Katsuyuki Shirai[a]

[a]Department of Radiology, Jichi Medical University Hospital, Tochigi, Japan; [b]Department of Radiology, Jichi Medical University Saitama Medical Center, Saitama, Japan; [c]Department of Otolaryngology, Jichi Medical University Hospital, Tochigi, Japan

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Nintedanib · Tyrosine kinase inhibitor · Multikinase inhibitor · Adverse event · Radiotherapy

Abstract
Since the launch of imatinib in 2001, tyrosine kinase inhibitors are being used in chemotherapy for a wide range of malignant tumors. Drugs that inactivate multiple molecular mechanisms are called multikinase inhibitors (MKIs). Nintedanib is a type of MKI that inhibits downstream cascades in three systems: vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived growth factor receptor inhibitions. It was initially developed as an anticancer drug for non-small-cell lung carcinoma; however, it was also found to inhibit the proliferation of fibroblasts associated with chronic inflammation in the lungs. Therefore, it is being more widely used to treat idiopathic pulmonary fibrosis, a benign disease, than as an antineoplastic agent. Several studies have reported adverse events associated with the concurrent use of MKIs with surgery or radiotherapy. Specifically, there has been a report cautioning against delayed wound healing associated with the use of nintedanib in patients undergoing surgery. However, there is no specific mention of its concurrent use during irradiation. We describe a case of a 72-year-old man with severely delayed recovery from radiation mucositis when nintedanib was being administered for benign disease.

Correspondence to:
Katsuyuki Shirai, kshirai@jichi.ac.jp

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Introduction

Tyrosine kinase inhibitors (TKIs) are drugs used to treat various cancers. TKIs that inactivate multiple molecular mechanisms, e.g., sunitinib or lenvatinib, are also called multikinase inhibitors (MKIs).

Currently, various MKIs have been applied in the treatment of solid tumors, either alone or in combination with cytotoxic drugs. In particular, MKIs with angiogenesis inhibitory effects have opened up new horizons in the treatment of hypervascular malignancies such as renal-cell and hepatocellular carcinoma, which have been difficult to treat with classical cytotoxic therapies. In the 2020s, the synergistic effects of TKIs and immune checkpoint inhibitors have also attracted attention; for example, Rizzo et al. [1, 2] reported that TKIs may reduce the number of tumor-associated macrophages, which act in a tumor-promoting manner through immunosuppressive, angiogenic, and cancer cell invasion-promoting effects. They also highlighted the possibility that TKIs promote the expression of MHC class I antigens in tumor cells and enhance the activity of killer T-cells [1, 2].

Nintedanib (BF1120) is one of oral MKI agents that inhibits downstream cascades in three main systems: the vascular endothelial growth factor receptor (VEGFr), fibroblast growth factor receptor (FGFr), and platelet-derived growth factor receptor [3]. This drug was developed as an anticancer agent [3]. However, its indication has been extended to benign diseases, owing to its fibrosis-inhibiting properties [4]. Currently, it is more widely used in the treatment for idiopathic pulmonary fibrosis (IPF) [5], a benign disease, than as an antineoplastic agent.

With inhibition of VEGFr and other cascades, MKIs interfere with angiogenesis of malignant neoplasms and occasionally inhibit wound healing of normal tissues or blood flow restoration in damaged tissues. Because they act on several pathways of normal cell proliferation, the adverse effects seen with MKIs are markedly distinct from those of classical cytotoxic chemoregimens: one such example being the high incidence of gastrointestinal perforation or tracheal fistula [6–9].

As nintedanib is no exception to this rule, caution is warranted for its use due to the possibility of delayed wound healing associated with surgery [5]. However, there is no specific mention in the product monograph regarding its use in combination with radiotherapy (RT) [5]. Therefore, we report a case of severely delayed recovery from radiation mucositis in a patient of head and neck cancer treated with RT who had been on nintedanib for complicated IPF.

Case Report

A 72-year-old man smoked up to 80 cigarettes per day for 40 years until he was 57 years old and quit smoking thereafter. Medical treatment for IPF was initiated at the age of 66 years. Due to the deterioration of his condition over time, manifested by shortness of breath on exertion and worsening of CT findings, nintedanib (300 mg/day twice daily) was recommended at the age of 70 years (Fig. 1a). Other comorbidities included type 2 diabetes and hyperlipidemia – both were well-controlled and stable. The Eastern Cooperative Oncology Group performance status score was 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature).

At 72 years old, approximately 2 years after nintedanib therapy was initiated, the patient was diagnosed with lateral wall oropharyngeal carcinoma with p16-positive cT2N1M0, stage I disease (Fig. 1b). An extended tonsillectomy and unilateral lymph node (level II to IV) dissection with composite resection of the external jugular vein was performed. Because the respiratory physician was concerned about the unpredictable effect of drug withdrawal, oral nintedanib was continued even on the day of surgery, and no withdrawal period was imposed.

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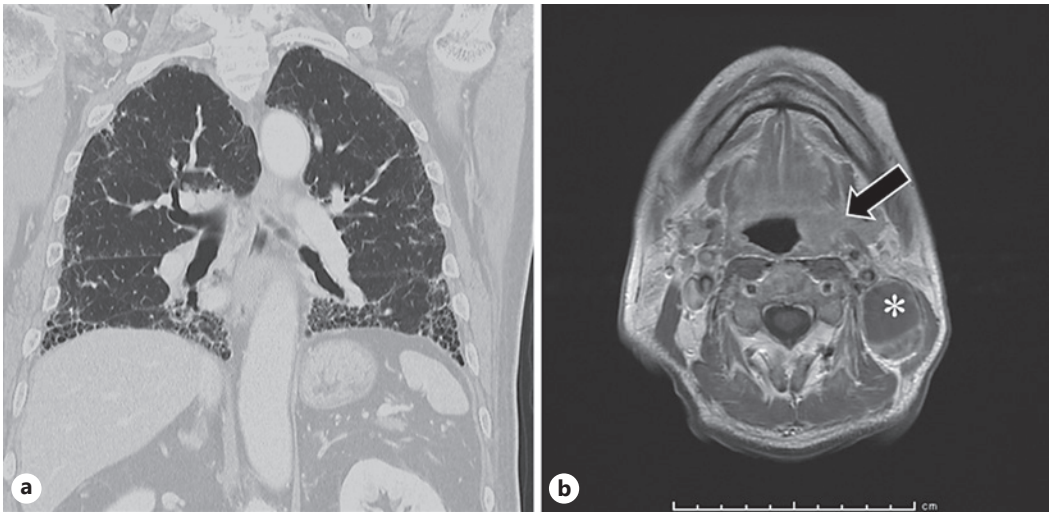

Fig. 1. Pre-treatment images of oropharyngeal carcinoma. **a** CT image of severe idiopathic pulmonary fibrosis (IPF). Contrast-enhanced T1-weighted fast spin-echo MR imaging (**b**) shows the primary tumor (arrow) and the bulky lymph node metastasis (asterisk).

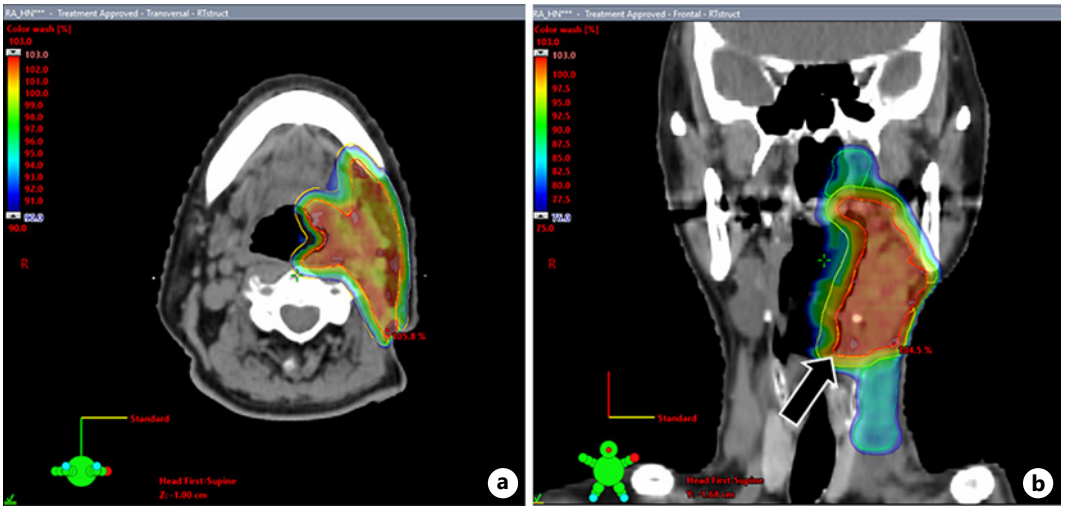

Fig. 2. Dose distribution of intensity-modulated RT (IMRT) with 66 Gy in 33 fractions. **a** Axial image. **b** Coronal image. Prolonged radiation mucositis was observed at the caudal edge with a positive surgical margin (arrow).

Perioperative wound healing was good, and endoscopy showed that the detached mucosa of the pharynx was almost normal and without any problems at 1 month postoperatively. Due to positive resection margins, postoperative RT was planned. No concurrent chemotherapy was administered due to the severe IPF. Intensity-modulated RT was performed with a radiation dose of 66 Grays (Gy) in 33 fractions (Fig. 2). According to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0., the patient had adverse events of grade 2 dysgeusia, dry mouth, pharyngeal mucositis, and grade 1 dermatitis during the RT period, all of which were expected. Acute pharyngeal mucositis, the most common adverse effect of head and neck RT, was first observed 2 weeks after the start of irradiation, when 20 Gy of radiation dose was delivered. Acetaminophen 1.6 g/day and celecoxib (200 mg/day) were the only analgesics used; no opioids were required. Based on the respiratory physician's recommendation, nintedanib

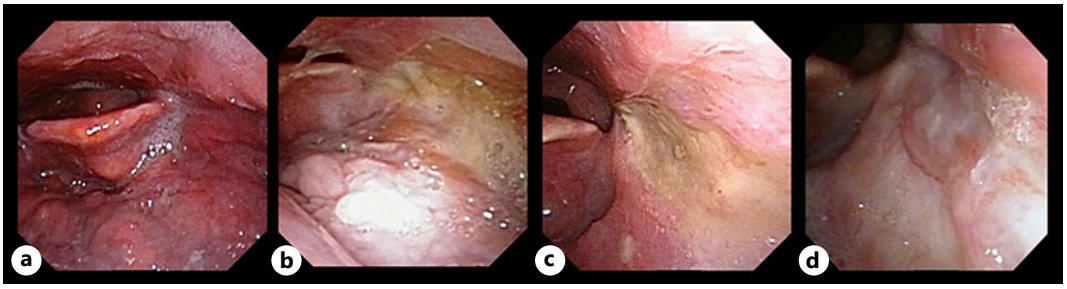

Fig. 3. Changes of radiation mucositis seen by endoscopy. **a** RT in progress (10 Gy), (**b**) day 46, (**c**) day 115, (**d**) day 344 after RT completion, respectively. Irregular surface fibrosis remains for long (**b**), with little recovery of the normal mucosal epithelium (**c**). Even 1 year later, there is no normal epithelialization, and residual inflammatory edema is seen in the surrounding area.

was not interrupted or reduced during RT (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000526077).

However, there was delayed healing of mucosa of the oropharynx and hypopharynx, with little to no recovery even after 2 months of treatment completion. After 59 days of RT completion, the patient required hospitalization due to local infection of the poorly healed mucosa. Antibacterial therapy with ampicillin/sulbactam was then administered. Severe odynophagia with mucosal inflammation was also observed, and at its peak, the oral morphine hydrochloride dose was increased to 40 mg/day. Finally, dose reduction for nintedanib, now suspected to be the cause for delayed recovery, was decided upon; the daily dose was reduced to 200 mg/day after 110 days from the completion of RT (online suppl. Fig. 1). No actinomycetes or fungal infections were consistently detected. The patient was discharged 119 days after RT; however, mucosal healing remained poor. The findings of nasopharyngoscopy revealed irregular fibrous epithelialization with an uneven tumor bed (Fig. 3). One year after treatment, the mucosa had not completely normalized, and the patient continued receiving acetaminophen (2.5 g/day) five times daily and oxycodone (15 mg/day) twice daily (grade 2 pharyngolaryngeal pain). In addition, late adverse events of grade 2 pharyngeal stenosis (pool of saliva) and grade 3 dysphagia (limitation of food types) persisted.

Regarding the primary disease, oropharyngeal carcinoma, there was no recurrence either at the primary tumor site or in the lymph nodes. IPF has been consistently well-controlled, with no progression or exacerbation of symptoms from the start of RT to date. For this report, we obtained written informed consent from the patient, for publication of details of their medical case and any accompanying images.

Discussion

This is a report of a rare case of exacerbation of a known adverse event of RT in a patient treated with MKI for a benign condition. Nintedanib is a small-molecule MKI that acts on three systems: VEGFr 1–3, FGFr 1–3, and platelet-derived growth factor receptor αβ. All three receptor cascades are considered to play important roles in activating tumor cell growth [3] as well as wound healing [10]. It was initially tested in clinical trials as an anticancer agent and approved for non-small-cell lung cancer in European Union countries in 2014 [11]. For other malignancies, a phase 3 trial of nintedanib plus carboplatin as a first-line of treatment for advanced ovarian cancer has been completed, and its efficacy and safety have been established in 2020 [11, 12].

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On the contrary, it was found that mitogenic action inhibits not only cancer growth but also fibrosis progression caused by chronic inflammation. This has paved the way for using it to treat chronic interstitial disease rather than malignant tumors, and it is now widely used to treat IPF in Europe, the USA, and Asia [4, 11]. Therefore, only indications for benign diseases, such as IPF, are covered by insurance in Japan. This was the first MKI agent used to treat benign diseases in this country.

It is well known that perforation of the gastrointestinal tract or fistulae in the trachea is a typical severe adverse event with bevacizumab. This monoclonal antibody agent inhibits the VEGFr signaling cascade with binding to the VEGF molecule. Furthermore, it has been suggested that a history of radiation therapy may increase this risk [13, 14]. However, more recently, concurrent risks with RT have been reported with ramucirumab, a similar monoclonal antibody agent. This binds directly to type 2 VEGF receptors and blocks the VEGFr downstream cascade [15, 16].

Moreover, several oral MKIs also share the commonality of inhibiting VEGFr, similar to bevacizumab. Numerous severe adverse events caused by the combination of conventional oral MKI and RT have been reported, including gastrointestinal or tracheal perforation caused by the combination of RT and sorafenib or sunitinib [6, 7], intestinal emphysema caused by the lenvatinib combination [11], and severe skin ulcers and fatal bleeding [17, 18] when combined with pazopanib. The most likely reason for these events is that ischemia and mitotic damage caused mainly by VEGFr inhibition add to the tissue damage caused by RT [9].

In addition to the VEGFr, nintedanib also inhibits the FGFr cascade. FGFr inhibition also has anticancer effects; however, it may affect normal wound healing by fibroblasts. The possibility of impaired wound healing has been particularly mentioned in the marketing insert for nintedanib. Indeed, a case of sudden wound dehiscence in a patient undergoing cardiac surgery has been reported [19]. As FGRr-blocking agents are relatively new, the clinical relevance of the interactions between FGFr inhibition and RT is yet to be fully understood. Therefore, the possibility that concurrent use of FGFr inhibitors and RT may be detrimental to tissue repair must be considered.

In this case, radiation therapy alone at 66 Gy in 33 fractions was administered to a postoperative high-risk patient with oropharyngeal cancer. Although concurrent cisplatin use is the standard therapy, chemoradiotherapy was dismissed due to severe IPF. Radiation mucositis during RT for head and neck cancer is a common adverse event. According to a study by Elting et al. [20], symptoms of radiation-induced mucositis generally improve within a few weeks after RT completion and rarely become chronic, except in cases of irradiation administered beyond the tolerated radiation dose. Oral or pharyngeal inflammation and associated pain flares gradually 2–3 weeks after the start of RT (20–30 Gy) and rapidly subside 2–3 weeks after completion [20]. The present case is a rare example of chronic mucositis caused by radiation alone, at the conventional dose. It is unusual for opioid use to continue for >1 year in case with complete response of the primary cancer to treatment. Although discontinuation of nintedanib due to mucositis was considered, it was continued at a reduced dose, owing to the following reasons: (i) unpredictable effects of abrupt discontinuation and (ii) difficulty of replacing nintedanib with other drugs. Pirfenidone, another drug for IPF, exhibits hepatotoxicity and photosensitivity, and the patient's job, as a construction site supervisor, would have been severely affected. Additionally, corticosteroids were feared to have adverse effects on preexisting diabetes and secondary liver damage.

It is noteworthy that the MKI was being used for benign disease and not for anticancer therapy. Drug administration for benign diseases is completely different from that of time-limited anticancer drug use in that it is often maintained for months to years. Therefore, its discontinuation or modification requires a completely different approach than that required for malignant diseases.

There were some limitations of this study. First, this case of concurrent RT with nintedanib was a novel experience for us, and we were relatively unfamiliar with the special characteristics of the drug. Nintedanib is a relatively new drug for IPF; the number of patients developing cancer during long-term use of this drug is still small. Second, this patient had other comorbidities, namely, type 2 diabetes and hyperlipidemia. Although well-controlled, the possibility of their influence cannot be ruled out. A more calibrated use of nintedanib during RT may develop with time after collective data are studied.

As an expert opinion, our observations on the case presented have led us to outline these preliminary recommendations: nintedanib use should always be monitored before RT in IPF patients. As with other VEGFr-inhibiting MKIs, discontinuation of nintedanib use may be considered during RT, for 1 week before and after treatment, if possible [9]. If there are associated complications, such as delayed mucosal recovery as observed in the present patient, it may be worthwhile to consider a longer withdrawal period. Substitution with other drugs or treatment modalities is another solution, if feasible. Finally, radiation oncologists need to be constantly aware regarding the introduction of new MKIs in benign diseases for an increasing range of conditions. In conclusion, we report a case of severe and prolonged radiation mucositis, after RT with nintedanib, for a benign disease; when administering RT, the status of MKIs used for nonmalignant disease should be carefully evaluated.

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Statement of Ethics

We obtained written informed consent from the patient, for publication of details of their medical case and any accompanying images. The Jichi Medical University Central Clinical Research Ethics Committee has determined that our project does not meet the "Common Rule" definition of human subjects' research and does not require CRB review. The certified review board number is 3200006.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Takahashi, Mori, and Shirai designed this study. Satoru Takahashi, Takafumi Nagatomo, Ryutaro Onaga, and Hiroshi Nishino were involved in patient management. Satoru Takahashi, Masashi Endo, Yukiko Fukuda, Kazunari Ogawa, Michiko Nakamura, Kohei Okada, Masahiro

Kawahara, and Keiko Akahane contributed to the analysis of the results. Hiroshi Nishino, Harushi Mori, and Katsuyuki Shirai supervised the project and approved the final manuscript.

Data Availability Statement

All data supporting the findings of this study have been included in this article and its online supplementary material. Further inquiries can be directed to the corresponding authors.

References

1 Rizzo A, Dadduzio V, Ricci AD, Massari F, Di Federico A, Gadaleta-Caldarola G, et al. Lenvatinib plus pembrolizumab: the next frontier for the treatment of hepatocellular carcinoma? Expert Opin Investig Drugs. 2022 Apr;31(4):371–8.
2 Rizzo A, Ricci AD, Gadaleta-Caldarola G, Brandi G. First-line immune checkpoint inhibitor-based combinations in unresectable hepatocellular carcinoma: current management and future challenges. Expert Rev Gastroenterol Hepatol. 2021 Nov;15(11):1245–51.
3 Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res. 2008 Jun;68(12):4774–82.
4 Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of Nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014 May;370(22):2071–82.
5 OFEV. (Nintedanib) [product monograph] [cited 2022 May 7]. Available from: https://www.boehringer-ingelheim.ca/sites/ca/files/documents/ofevpmen.pdf.
6 Inoue T, Kinoshita H, Komai Y, Kawabata T, Kawa G, Uemura Y, et al. Two cases of gastrointestinal perforation after radiotherapy in patients receiving tyrosine kinase inhibitor for advanced renal cell carcinoma. World J Surg Oncol. 2012 Aug;10(1):167.
7 Basille D, Andrejak M, Bentayeb H, Kanaan M, Fournier C, Lecuyer E, et al. Bronchial fistula associated with sunitinib in a patient previously treated with radiation therapy. Ann Pharmacother. 2010 Feb;44(2):383–6.
8 Toda S, Iwasaki H, Murayama D, Isoda M, Nakayama H, Suganuma N, et al. Pneumatosis intestinalis associated with lenvatinib during thyroid cancer treatment: a case report. J Med Case Rep. 2021 Nov;15(1):556.
9 Murakami Y, Kenjo M, Ishikawa K, Sakayauchi T, Itasaka S, Negoro Y, et al. Risk factors for severe gastrointestinal toxicity in patients receiving palliative radiotherapy for metastatic bone tumors: association with the use of molecular-targeted agents. J Radiat Res. 2020 Jul;61(4):629–34.
10 Grazul-Bilska AT, Johnson ML, Bilski JJ, Redmer DA, Reynolds LP, Abdullah A, et al. Wound healing: the role of growth factors. Drugs Today. 2003 Oct;39(10):787–800.
11 Khalique S, Banerjee S. Nintedanib in ovarian cancer. Expert Opin Investig Drugs. 2017;26(9):1073–81.
12 Ray-Coquard I, Cibula D, Mirza MR, Reuss A, Ricci C, Colombo N, et al. Final results from GCIG/ENGOT/AGO-OVAR 12, a randomised placebo-controlled phase III trial of nintedanib combined with chemotherapy for newly diagnosed advanced ovarian cancer. Int J Cancer. 2020;146(2):439–48.
13 Hapani S, Chu D, Wu S. Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis. Lancet Oncol. 2009 Jun;10(6):559–68.
14 Kim N, Choi SH, Chang JS, Kim YT, Kim SW, Kim GM, et al. Use of bevacizumab before or after radiotherapy increases the risk of fistula formation in patients with cervical cancer. Int J Gynecol Cancer. 2021 Jan;31(1):59–65.
15 Akahane K, Shirai K, Wakatsuki M, Ogawa K, Minato K, Hamamoto K, et al. Severe esophageal stenosis in a patient with metastatic colon cancer following palliative radiotherapy, ramucirumab, and chemotherapy. Clin Case Rep. 2020 Mar;8(5):919–22.
16 Lee YL, Hsu JF, Yang CJ. Tracheoesophageal fistula in a patient with advanced non-small cell lung cancer who received chemoradiotherapy and ramucirumab. J Thorac Oncol. 2019 Jan;14(1):e17–8.
17 Uwa N, Terada T, Mohri T, Tsukamoto Y, Futani H, Demizu Y, et al. An unexpected skin ulcer and soft tissue necrosis after the nonconcurrent combination of proton beam therapy and pazopanib: a case of myxofibrosarcoma. Auris Nasus Larynx. 2017 Aug;44(4):484–8.
18 Kawasaki K, Hamamoto Y, Fukada J, Adachi M, Sasaki H, Takaishi H, et al. Fatal hemorrhage in a patient with advanced soft tissue sarcoma following radiation and pazopanib treatment: a case report. Oncol Lett. 2016 Apr;11(4):2408–10.
19 He C, Raman J. Wound dehiscence with nintedanib after cardiac surgery: a cautionary tale. JTCVS Tech. 2021 Nov;6:99–101.
20 Elting LS, Cooksley CD, Chambers MS, Garden AS. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys. 2007;68(4):1110–20.